REMARKS

Claims 1-12 are pending in the instant application. Claims 1-12 have been rejected. Applicants respectfully point out that only claims 1-4 and 6-12 are mentioned specifically as being rejected in the instant Office Action. However, Applicants have addressed the rejection as pertaining to all pending claims. Claims 10-12 have been cancelec. Claims 1, 4, 8 and 9 have been amended. No new matter has been added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Rejection of Claims Under 35 U.S.C. 112, First Paragraph

Claims 1-4 and 6-12 have been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The Examiner acknowledges that the specification is enabling for 1) a method of inhibiting corneal allograft rejection in a mouse or human comprising the administration of an antisense oligonucleotide between 8-50 nucleotides in length that targets and inhibits the expression of

ICAM-1; and 2) methods of preserving a corneal explant in vitro comprising incubation of explanted cornea in a composition comprising OPTISOL and an antisense oligonucleotide between 8-50 nucleotides in length that targets and inhibits expression of ICAM-1, VCAM-1, or ELAM-1. The Examiner suggests, however, that the specification as filed fails to provide enablement for methods of inhibiting corneal allograft rejection in an organism comprising administering antisense compounds targeted to ELAM-1 or VCAM-1, nor does it provide enablement for methods of preserving a corneal explant comprising an antisense oligonucleotide in the absence of OPTISOL. Applicants respectfully traverse this rejection.

With respect to the Examiner's comments regarding the claims directed to methods of *ex vivo* treatment of corneal explants, Applicants disagree with the Examiner's suggestion that the use of OPTISOL is necessary for enablement of the claimed invention. Although the working examples provided in the specification for preservation of explants used OPTISOL in conjunction with antisense compounds of the instant invention, as the Examiner indicates in the Office Action itself at page 5, a variety of storage media and techniques have been proposed. As also taught in Example 23, beginning at page 54, OPTISOL is merely a corneal storage medium. The title of the example also makes clear that the oligo is being

evaluated in a "storage media". Therefore, limiting the claims to only one such media would not be consistent with what has been taught in the specification, shown in the art and what would be known by one of skill. Other media or vehicles for delivery of the antisense compounds to the explants would also be possible based on the teaching in the prior art cited by the Examiner. In an earnest effort to advance the prosecution of this case, Applicants have amended the claims to recite that the method involves use of a corneal storage medium as well as the antisense compounds of the instant invention.

With respect to the Examiner's rejection of the claims relating to a method of inhibiting corneal allograft rejection comprising administering one of three adhesion modulating molecules (ICAM-1, VCAM-1, ELAM-1), Applicants respectfully disagree with the Examiner's suggestions that antisense is inherently unpredictable.

The Examiner has pointed to articles concerning the technology of antisense oligonucleotides to support the view that antisense technology is unpredictable and that predicting efficacy based on *in vitro* data is problematic. However, when one reads each of the papers as a whole, as required under MPEP 2141.02, these references actually teach the potential usefulness of this class of drugs in humans, and more importantly fail to provide any reasonable basis

to doubt the pharmacological activity observed in cells in the instant invention would also occur in humans. Therefore, what these papers cited by the Examiner actually teach is that antisense oligonucleotides must be developed using well designed studies that progress logically from activity in cells to activity in animals, and then to testing in humans. Nowhere in the references cited do the authors state or suggest that results of well-designed *in vitro* pharmacological studies would not be predictive of activity in humans. With the results of in vitro inhibition of ELAM-1 and VCAM-1 that are presented in the instant specification as filed, one of skill would be able to extrapolate those data to predict *in vivo* efficacy.

Branch (1998) is cited by the Examiner in support of his position. This older paper regarding the technology of antisense teaches the need to develop antisense molecules based on sound data and careful screening, such as is presented in the instant specification. Nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects in humans is unpredictable. The Examiner, however, attempts to use this paper to support suggestions concerning the inaccessibility of most potential target RNA binding sites to antisense molecules and the unpredictability of antisense effects. One of skill in the art would not expect to

predict the "winning" antisense compound *a priori*, but would screen a reasonable number of compounds in order to find the one best suited to his or her needs. Time and difficulty of experiments are not determinative of enablement if they are merely routine. Quantity of examples is only one factor that must be considered before reaching the final conclusion that undue experimentation would be required. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.(MPEP 2164.06). The fact that effective antisense drugs are selected from large pools of candidates and then optimized, rather than predicted *a priori*, does not indicate lack of enablement, *i.e.*, the need for undue experimentation. "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

Furthermore, the need to select an antisense compound from a pool of candidates is not unique to antisense drugs; all drugs are selected from large pools of candidates. Only five in 5,000 compounds make it from early research and preclinical testing to

clinical trials, and of those five that enter clinical trials only one is approved (data from PhRMA, Pharmaceutical Research and Manufacturers of America).

The paper by Palu et al. (1999) is a review paper on the technology of gene therapy, not antisense. Gene therapy is an entirely different technology with its own set of issues for drug development. Citing this paper to support the unpredictability of antisense is inappropriate. Nowhere does this paper state that extrapolation from *in vitro* data on antisense compounds to *in vivo* effects is unpredictable.

The paper by Agrawal and Kandimalia (2000) is another review paper on the technology of antisense. Nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable.

The paper by Chirila et al. (2002) is a review of the use of polymers for delivery of antisense compounds. Although this paper reviews problems that have arisen during development of antisense, problems that are addressed and solved in the specification as filed, nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable.

Finally, the press release cited by the Examiner does not support the conclusion that data from *in vitro* studies is not

predictive of *in vivo* activity. This failure of a clinical trial for Crohn's disease is a very different standard where a drug must be statistically significantly better than a placebo on a particular endpoint. It does not mean the drug was without activity to inhibit gene expression when results from *in vitro* studies are extrapolated to *in vivo* activity.

Further, the Examiner has failed to support the proposition that administration of antisense to VCAM-1 or ELAM-1 would be unpredictable based on any objective evidence. In contrast, data are provided in the specification as filed showing the selection and design of antisense oligonucleotides to selected targets and their activity *in vitro*. Therefore, Applicants have clearly met their burden under 112, first paragraph. Further, Applicants respectfully remind the Examiner that the "absence of working examples should never be the sole reason for rejecting the claimed invention on the grounds of lack of enablement and the specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation". In re Borkowski, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970)). (MPEP 2164.02).

However, in an earnest effort to advance the prosecution of this case, Applicants have canceled claims 10-12. Withdrawal of this rejection is respectfully requested.

II. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

Jane Massey Licata
Registration No. 32,257

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Licata & Tyrrell P.C.
66 E. Main Street
Marlton, NJ 08053
856-810-1515